Problems with ethical approval, and how to fix them

Mendel, Jonathan; Goldacre, Ben; Ernst, Edzard; Whittle, Samuel

Published in:
BMJ

DOI:
10.1136/bmj.i4626

Publication date:
2016

Document Version
Peer reviewed version

Problems with ethical approval, and how to fix them: lessons from three trials in rheumatoid arthritis

Corresponding author (and this manuscript's guarantor): Jonathan Mendel

(Geography, School of Social Sciences,

University of Dundee, Nethergate, Dundee, DD1 4HN, UK

E-mail: j.m.mendel@dundee.ac.uk; Tel: 01382 385083)

Ben Goldacre (Centre for Evidence-Based Medicine, University of Oxford, Oxford, UK)

Edzard Ernst (Peninsula Medical School, University of Exeter, Exeter, UK)

Samuel Whittle (Discipline of Medicine, University of Adelaide, Australia)

Keywords: ethics, homeopathy, ocrelizumab, placebo, rheumatoid arthritis

Word count: 3,257 (excluding title page, data sharing statement, declaration of interests, figures, boxes and tables).

Ethical approval: this research did not require ethical approval (Jonathan Mendel discussed this with Geography at the University of Dundee, and they confirmed that this was not needed).

Transparency declaration: Jonathan Mendel affirms that the manuscript is an honest, accurate, and transparent account of the research being reported; that no important aspects of this have been omitted; and that any discrepancies from the research that was planned have been explained

Introduction

Internationally, clinical trials are subject to costly and onerous regulation which aims to ensure trials are well designed, with risks to participants minimised wherever possible, and any significant outstanding risks communicated clearly to participants. We set out to assess how well current regulatory frameworks meet these aims, and the extent to which the relevant regulatory documentation can be accessed for independent scrutiny.

A recent study reported that over 10,000 Rheumatoid Arthritis (RA) patients have been randomised to control groups receiving ineffective treatments in trials of biologic disease-modifying antirheumatic drugs (bDMARDs), risking "irreversible deterioration in condition".[1] We investigated the process of ethics approval, and the information given to patients, for two trials of ocrelizumab included in this report.[1] We also reviewed documents for one homeopathy trial on RA, as problems with ethics approval and informed consent in complementary and alternative medicine (CAM) have been reported.[2] Below we describe the methods we used in attempting to obtain relevant documents, the barriers we faced, and the ethical shortcomings we identified. RA is a common disease for which many new therapies have been developed over the last 2 decades; it is therefore an exemplary setting for exploring these issues, which are relevant to clinical trials of interventions in all areas of medicine.

Barriers to accessing ethics documents

The STAGE [3] and FEATURE [4] trials of ocrelizumab were selected as examples of trials that raised questions around ethics approval in bDMARD research, drawing on Estellat and Ravaud's [1] analysis of a large sample of protocols in this field and SW's expert opinion. Genentech/Roche were the sponsors of both studies. We approached the sponsors by email and phone to: (1) ask about the justification for using a placebo control group; (2) request copies of documents and correspondence with the ethics committee on this issue; and (3) request copies of documents given to participants (specifically a blank template consent form and patient information sheet). We also approached the UK Health Research Authority overseeing these trials for the same information, using the UK Freedom of Information Act (FoIA).

A trial of homeopathy in RA at Wrightington, Wigan and Leigh NHS Foundation Trust was highlighted on social media [5]*** as an interesting example of ethical problems in Complementary and Alternative Medicine (CAM) research. We approached the Trust using FoIA to request a copy of all documents submitted to the REC about this trial, and all subsequent correspondence to and from the REC about this trial, as well as copies of the information given to patients.

Before any issues around approval or communication with participants could be assessed, there were extensive delays and challenges obtaining documents and information, for all three trials. We initially requested documents on the two ocrelizumab trials from Roche, the sponsor. Roche stated that the Association of the British Pharmaceutical Industry (ABPI) code of conduct – which prohibits commercial promotion of drugs directly to patients – forbade them from sharing documents with us. The originator of our request, JM, is a university lecturer. Although not a healthcare professional himself, the request gave his academic email address as his contact, explained that he was researching the use of placebo comparators in RA research, and asked questions about placebo comparators (rather than any active treatment). We believe it was clear that he was not seeking personal medical advice and were surprised to see this regulation being cited as a reason not to share information such as how the use of placebo comparators was presented to trial participants. A quote from Roche's refusal is given below:

> "[We] do not want to appear unhelpful or evasive…we can only advise healthcare professionals directly with regard to either clinical information or specific trials in progress for any Roche product. This is because this information is strictly contrary to the…ABPI…Code of Practice regulations. Therefore, as a pharmaceutical company, Roche is limited as to the level of information we can provide to members of the public directly.... [We refer you to] clause 23.4 (including the supplementary information) of the ABPI Code of Practice [which] covers the provision of information to the public….it is important that pharmaceutical companies do not provide advice on personal medical matters for prescription only medicines…The reason for this is to ensure that pharmaceutical companies do not interfere with the patient/doctor or patient/prescriber relationship by offering advice or information which would undermine that of either the doctor or other prescriber."

BG (one of three medical doctors on the project) then contacted Roche directly, with more success. However this slowed the process down, and could be more of a problem for other teams of legitimate researchers which may not include clinicians. Furthermore, while Roche did subsequently send us parts of the documentation from the ethics approval process, as analysed below, when we went on to ask for copies of all correspondence with this Ethics Committee, to see how specific issues were addressed by that body, Roche once again declined, on this occasion explaining that they were "unable to provide it as ocrelizumab is undergoing regulatory assessment and this information forms part of the confidential filing dossier." We finally used a FoIA request to try to access these documents via the Health Research Authority (HRA), with more success, although we are still missing documents which might be informative.

There were also problems accessing documents from the Trust responsible for the homeopathy trial. They replied promptly, but a large number of key requested documents were missing (including the research protocol or project proposal, the Participant Information Sheet, and the Participant Consent Form). When these were supplied, it seemed that there was additional correspondence between the REC and investigators that had not been sent; when we queried this (and emphasised that it should have been supplied in response to our original request) some further information was then supplied. This additional information made clear that there were further additional important documents related to this process (for example, the Participant Information Sheet was changed after discussions with the REC). After extensive correspondence (which also brought delays) we eventually received all the requested information.

Issues with the trials

The documentation received on the ocrelizumab trials was reviewed by 3 authors (JM, BG and SW) and the documentation on the homeopathy trial by 3 authors (JM, BG and EE) in order to assess how the use of a placebo comparator was justified; how well the trial processes met with ethical expectations for research on human participants; and whether adequate information on shortcomings or risks with the comparator was given to patients.

Problems with risk mitigation: ocrelizumab trials

FEATURE and STAGE randomised patients with active RA and inadequate responses to methotrexate to treatment with either ocrelizumab or placebo plus methotrexate for up to 48 weeks, before re-randomisation to active therapy or entry into open-label treatment with ocrelizumab. As rituximab (a bDMARD with the same molecular target as ocrelizumab) was an established therapy for active RA, this potentially deprived the participants of an effective therapy for as much as a year. Inadequate treatment of RA can lead to irreversible structural damage, additional pain and functional impairment.

The ethics application for FEATURE argues that “[r]einstatement of treatment with methotrexate is frequently effective”, but we would question its argument:

- FEATURE’s ethics application acknowledges that “the main ethical concern with this study is the need for the control arm to receive placebo ocrelizumab infusions. However, this group will receive methotrexate throughout the trial, which is considered standard first-line therapy in many institutions and the participants can

continue with analgesics, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and steroids if receiving these medications at a stable dose prior to the trial." Methotrexate is used as first-line treatment, but participants here had already failed treatment with methotrexate and were therefore no longer at the 'first-line' stage.

- The applicants quote Kapral et al. [6] as evidence that methotrexate is an effective DMARD, even in those for whom it has previously been ineffective. However, the findings of this single cohort study cannot be readily generalised and the initial dose of methotrexate employed (median 10mg) was much lower than in FEATURE (16.3mg at baseline). Most patients in Kapral's cohort whose initial dose of methotrexate was similar to that in FEATURE failed 're-employment' due to inefficacy. Instead of this reliance on Kapral et al., discussion of risk mitigation could have been grounded in a review of the available evidence.
- Rescue therapy was permitted but not mandated. The presence of real or perceived barriers to treatment escalation via rescue therapy is supported by the fact that only 26% of placebo-treated participants in STAGE received rescue drugs, despite very active disease at baseline and previous failure to respond to methotrexate. Furthermore, only 27.6% of the placebo group achieved an ACR20 response at week 48 (a 20% improvement in a composite measure of disease activity, equivalent to a minor clinical response).
- Participants in STAGE who received the active drug achieved a significant structural benefit compared to controls, confirming that placebo patients were disadvantaged despite the availability of rescue therapy. This risk could have been mitigated if other bDMARDs with evidence of effectiveness had been used as comparator.

A Research Ethics Committee (REC) looking at FEATURE asked for "clarification regarding whether the patients in the placebo arm would be deprived of other treatment options". However, they appear to have accepted reassurance that "patients would be able to take additional medications (NSAIDS and steroids) as needed, and that there were many options for escape therapy". We cannot find any further evidence of discussion on this key issue by the REC, nor evidence of discussion of a bDMARD as an active comparator (despite their widespread use at this stage of disease).

Problems with risk mitigation: homeopathy

The REC form for the homeopathy trial is inconsistent with the research protocol on important features (see box 3) but there is no evidence that the REC raised this. Moreover, some of the exclusion criteria of this trial (taking DMARDS or breastfeeding) seem

unjustified: homeopathic remedies beyond the C12 potency (i.e. diluted 12 times at a ratio 1: 100 resulting in a final dilution of 1: 10000000000000000000000000) contain no active molecules to interact with DMARDs or breastfeeding. Patients may conceivably have been disadvantaged by acting on these exclusions.

Failure to communicate risks of placebo during informed consent: ocrelizumab

Roche supplied only an excerpt from an application to a UK REC for the FEATURE study. This recognised that "the main ethical concern with this study is the need for the control arm to receive placebo ocrelizumab infusions". However, the REC failed to ensure participants were told this. There is room for professional debate on the extent of specific risks, and it is not necessary to share all information seen by the REC with participants. However it is important that participants are aware of major issues with the research so that they can make an informed choice: the fact that the control group treatment was seen as the 'main ethical concern' with the study strongly suggests this issue was sufficiently important that it should have been shared with participants. At the very least one might expect to see discussion on whether this information should be shared. Additional risks to members of the placebo control group such as increased pain, impairment and permanent structural damage were not made explicit in the STAGE or FEATURE consent forms. Also, while the risks of corticosteroids are explained, the consent forms do not make explicit the risks of increased doses as rescue therapy.

Failure to communicate methodological shortcomings and the results of previous research: homeopathy

The homeopathy trialists outlined a procedure for soliciting informed consent which was approved by the REC. However, the information provided was problematic. The patient information (as revised after REC review) stated that homeopathic remedies are "usually based on minerals or herbs". This implies that homeopathic remedies contain active ingredients, but remedies beyond the C12 potency (or rather, dilution) contain no active molecules. The patient information (as revised after REC review) stated that "there is currently little clinical evidence about the efficacy of homeopathic remedies" but did not state that the totality of the evidence fails to show that homeopathic remedies are effective beyond placebo.[7]

The patient information states that the "research <u>may</u> benefit you or future patients because the findings will inform treatment". The sponsoring NHS trust declared that "an appropriate

process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality". However, it is hard to see how a small non-randomised trial of homeopathy – which, the REC noted, covers similar ground to previous higher-quality trials – will alter current best evidence. While some or all patients may still have made an informed choice to participate, knowing the shortcomings, the REC form does not discuss whether the study is a good use of patients' time or NHS resources.

Lack of systematic presentation of evidence to REC

The ethics documentation for FEATURE refers to a single observational study [6] when emphasising the potential benefits of methotrexate in the control group. Even making the problematic assumption that patients in Kapral et al. were very similar to FEATURE participants, this is inadequate. Numerous evidence-based therapies for patients with RA who have failed to respond to methotrexate could have been used as direct comparators. The failure by applicants to provide, and by reviewers to expect, robust systematic reviews on the effectiveness of the experimental and control treatments is likely to have undermined the reasoning that informed approval of this trial. Similarly, the homeopathy trial's REC form suggests uncertainty about whether homeopathy is effective, which conflicts with best available evidence.

Summary

In three example trials, we found serious problems with the ethics review and informed consent process. We also encountered barriers to accessing the information necessary to make such an appraisal. Our investigation suggests it is naïve to accept REC approval alone as evidence that ethical issues have been appropriately reviewed, with the trial appropriately designed, best evidence considered, and harms minimised. Similarly, it is naïve to accept statements that informed consent was obtained as evidence that participants were given the information that a broader range of clinicians, researchers and patients would regard as appropriate for informed consent. We recognise that there is room for disagreement on the specific concerns raised by any individual trial or document, but we argue that a better route is transparency: it should be straightforward for anyone to access and critically appraise the details of the ethical review that has taken place, and the actual information given to patients. At present, there are significant barriers to accessing the relevant documents.

These issues are important throughout medicine. In our experience, similar methodological shortcomings are characteristic of many studies of biological DMARDs (see [1]), of CAM

(see [2]), and of other areas of medical research. In this paper we consider two Roche trials and one homeopathy trial, but we do not believe that these were uniquely problematic; instead, they are used to illustrate what appear to be widespread issues. It is highly unlikely that, for example, barriers to accessing the relevant documents are unique to these three trials. While a systematic review of a larger sample of trials would be desirable, the difficulties in even accessing basic ethics documents – and the time taken to do so – means that without reform such scrutiny is not likely to be feasible.

Poor regulation of research can cause direct harm to patients. It can also undermine the credibility of research, making recruitment harder. However, the failings identified here are amenable to improvement through established means. We suggest the following, which reflect established recommendations for medical research:

1. Systematically review the evidence relating to current and proposed treatments. In most cases it is impossible to build a robust understanding of the possible utility, risks and benefits of a proposed trial without looking at what is already known about the topic. In the examples above, the use of a systematic review could have ensured a much clearer picture of the evidence was available to the REC and participants. While we appreciate that a systematic review is not sufficient for ensuring that improvements take place (for example, investigators might produce a highly biased review) having such a review available for critical scrutiny will be an improvement on the status quo and would, as discussed below, allow more effective scrutiny by RECs and others.

2. Assess the quality of the proposed research, and tell patients about this. Ideally, RECs or other appropriate bodies should conduct critical evaluations of both the quality of the evidence submitted by investigators (for example, their systematic reviews) and of the research proposal. While judging research quality can be challenging and there will be a significant grey area, some trials are sufficiently unlikely to prove informative that RECs should be able to make a clear negative assessment. If the ethics process permits poor-quality research at all, the limitations of the research should be made explicit to patients so they can make an informed choice about participation. This might become part of what Chalmers describes as a “patient-led good controlled trials guide” [8].

3. Ensure that risks are appropriately mitigated (including risks associated with placebo).

4. Give patients a summary of existing evidence on the intervention and of any risks of participation. Where patients face risks from participation in a trial, or where previous research casts doubt on a therapy’s plausibility, this should be clearly and explicitly explained.

5. Make all documentation around ethics approval and consent freely available. Blank consent forms should be made publicly available alongside trial registration, accompanied by the participant information sheet. Similarly, correspondence with RECs and other bodies taking on a similar role should routinely be made publicly available. This will allow ethics processes to be independently reviewed, publically discussed, and learnt from.

Larger-scale research is needed to investigate the prevalence of the problems we have identified with ethics approval and informed consent. Larger studies would allow one to benchmark or assess differences between RECs and facilitate accountability for individual committees. At minimum, a review of transparency policies for institutional and national ethics review bodies is needed. Ethics processes are important to society, and should be open to public scrutiny. Openness is vital, both to minimise avoidable participant harms and to maintain public trust.

Data sharing statement: We are happy publish anonymised copies of the responses we received in response to our requests for ethics documentation in BMJ, alongside the article, assuming BMJ can resolve any potential issues re copyright.

References

1 Estellat C and Ravaud P. Lack of head-to-head trials and fair control arms: randomized controlled trials of biologic treatment for rheumatoid arthritis. *Arch Intern Med* 2012; 172(3): 237-44.

2 Lim B, Schmidt K, White A, et al. Reporting of ethical standards: differences between complementary and orthodox medicine journals? *Wien Klin Wochenschr* 2004;116(14): 500-503.

3 ClinicalTrials.gov registration number NCT00406419. Registration date 30/11/2006.

4 ClinicalTrials.gov registration number NCT00673920. Registration date 5/5/2008.

5 Scott B (bmds). Saw this whilst waiting to see a surgeon at Wrightington hospital yesterday. 22 April 2015, 1102. Tweet. Available from https://twitter.com/bmds/status/590818022396403712

6 Kapral T, Stamm T, Machold K P, et al. Methotrexate in rheumatoid arthritis is frequently effective, even if re-employed after a previous failure. *Arthritis Res Ther* 2006; 8(2): R46.

7 National Health and Medical Research Council. NHMRC Information Paper: Evidence on the effectiveness of homeopathy for treating health conditions. Canberra: National Health and Medical Research Council 2015.

8 Chalmers I. A patient-led good controlled trials guide. *Lancet* 2000; 356: 774.

Contributorship:

JM and BG conceived the study. JM wrote the first draft. SW led on critiquing the Roche trials, EE on critiquing the homeopathy trial. All authors revised and extended the paper.

Acknowledgements:

Our thanks to: Candice Estellat and Phillippe Ravaud for data sharing; Estellat for broader discussions; Iain Chalmers for helpful suggestions; and HRA, Roche, Wrightington, Wigan and Leigh NHS Foundation Trust and Genentech for the information they shared. JM's

contribution benefited from discussions about ethics with Yvonne Hail, Nicholas Fyfe, Alison Reeves, and in Dundee's Social Research Methods MSc classes.

Competing Interests:

BG reports personal fees/additional income from speaking and writing for lay audiences on problems in science and medicine including, as a minor theme, problems with ethics review. BG reports grant funding from the LJAF, Wellcome, Health Foundation, and NIHR, outside the submitted work.

EE has nothing to disclose.

JM reports grant funding from Oak Foundation, grants and other from Scottish Institute for Policing Research and grants and other from Scottish Crucible, outside the submitted work. JM has received a very small additional income (under £150 in total) for writing about problems around evidence and policy.

SW reports grants from Daiichi Sankyo, personal fees and non-financial support from AbbVie, personal fees and non-financial support from Pfizer, personal fees and non-financial support from UCB, personal fees from Janssen, personal fees from Menarini, personal fees from AstraZeneca, personal fees from Bristol-Myers Squibb, outside the submitted work; and SW works in an academic rheumatology unit that participates in industry-sponsored pharmaceutical clinical trials.

Box 1 – inconsistencies in homeopathy ethics documentation

The homeopathy trial REC form states that patients taking DMARDs or who have used homeopathy in the past six months are excluded; however, the only exclusions mentioned on the research protocol are people who are “under 18, have previous experience of homeopathic treatment, are pregnant or breast feeding or have severe co-morbidities that might affect RA treatment.” The REC form, in turn, does not mention an exclusion of people who are breastfeeding or of under-18s.